Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Seretide (salmeterol/fluticasone propionate)

SE/W/005/pdWS/002

Rapporteur:	SE
Finalisation procedure (day 120):	130318
Date of finalisation of PAR	130515

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Seretide Diskus/Viani Diskus
INN (or common name) of the active substance(s):	Salmeterol/fluticasone propionate
MAH (s):	GlaxoSmithKline R&D
Pharmaco-therapeutic group (ATC Code):	R03AK06
Pharmaceutical form(s) and strength(s):	Inhalation powder

I. EXECUTIVE SUMMARY

Based on the clinical data submitted by the MAH a SmPC change is proposed in section 5.1.

Summary of outcome

☐ No change

☐ Change

☒ New study data: section 5.1

☐ New safety information

☐ Paediatric information clarified

☐ New indication

II. RECOMMENDATION[1]

Based on the studies submitted for this paediatric worksharing procedure an update of Section 5.1 of the SmPC is proposed.

III. INTRODUCTION

The MAH submitted four completed paediatric studies for salmeterol/fluticasone propionate, in accordance with Article 46 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Seretide and that there is no consequential regulatory action.

[1] *The recommendation from section V can be copied in this section*.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical studies

Seretide is a combination product containing, salmeterol xinafoate and fluticasone propionate. The active substances are well-known and belong to the Pharmacotherapeutic Group: Adrenergics and other anti-asthmatics. Seretide is provided as a pressurised metered dose (MDI) inhaler, i.e. Seretide Evohaler or Viani Evohaler, or a dry powder inhaler (DPI), i.e. Seretide Diskus or Viani Diskus.

Seretide Evohaler/Viani Evohaler and Seretide Diskus/Viani Diskus are approved in EU countries either through mutual recognition (MR) procedures (SE/H/169/01-03, SE/H/170/01-03, UK/H/392/01-03, UK/H/398/01-03) or by national procedures. The paediatric indication was already included in the original approval for Seretide Diskus/Viani Diskus and via Type II variation (UK/H/0392/01-03/W10, UK/H/0398/01-03/W12) for Seretide Evohaler/Viani Evohaler.

The approved MR indication for paediatrics is:

Asthma
Salmeterol/Fluticasone propionate is indicated in the regular treatment of asthma where use of a combination product (long-acting beta-2-agonist and inhaled corticosteroid) is appropriate:

- Patients not adequately controlled with inhaled corticosteroids and ‘‘as needed’’ short-acting beta-2-agonist

or

- Patients already adequately controlled on both inhaled corticosteroid and long-acting beta-2-agonist.

Note: Seretide 50 microgram/100 microgram strength is not appropriate in adults and children with severe asthma. (*only DPI*)

The approved MR posology for paediatrics is:

Recommended dosage in asthma

Adults and adolescents 12 years and older

For the MDI, i.e. for Seretide/Viani Evohaler
-2 inhalations of 25 micrograms salmeterol and 50 micrograms fluticasone propionate twice daily
-2 inhalations of 25 micrograms salmeterol and 125 micrograms fluticasone propionate twice daily
-2 inhalations of 25 micrograms salmeterol and 250 micrograms fluticasone propionate twice daily

or

For the DPI, i.e. for Seretide Diskus/Viani Diskus
-1 inhalation of 50 micrograms salmeterol and 100 micrograms fluticasone propionate twice daily
-1 inhalation of 50 micrograms salmeterol and 250 micrograms fluticasone propionate twice daily
-1 inhalation of 50 micrograms salmeterol and 500 micrograms fluticasone propionate twice daily

Children 4 years and older

For the MDI, i.e. for Seretide/Viani Evohaler
-2 inhalations of 25 micrograms salmeterol and 50 micrograms fluticasone propionate twice daily

or

For the DPI, i.e. for Seretide Diskus/Viani Diskus
-1 inhalation of 50 micrograms salmeterol and 100 micrograms fluticasone propionate twice daily

IV.2 Non-clinical aspects

N/A

IV.3 Clinical aspects

1. Introduction

The MAH submitted reports for:

- ADA109055: A 52-week, Randomized, Double-Blind, Parallel-Group Study of Fluticasone Propionate/Salmeterol DISKUS™ Combination Product (FSC) 250/50 mcg BID and Fluticasone Propionate (FP) DISKUS 250 mcg BID in Treatment of Subjects with Asthma
- ADA109057: A 52-week, Randomized, Double-Blind, Parallel-Group Study of Fluticasone Propionate/Salmeterol DISKUS™ Combination Product (FSC) 250/50 mcg BID and Fluticasone Propionate (FP) DISKUS 250 mcg BID in Treatment of Subjects with Asthma
- SAM101667: A multicentre, randomized, double blind, parallel group study to compare the efficacy and safety of Salmeterol/Fluticasone propionate combination product (SERETIDE®) 50/100mcg with Fluticasone propionate (FLIXOTIDE®) 200mcg, both delivered twice daily via the DISKUS® inhaler, in the treatment of children aged 6-16 years with symptomatic asthma.
- ADA113872: A Randomized, Double-Blind, Parallel Group study of FSC 100/50 and FP 100, both twice daily, in a Pediatric Population during the Fall Viral Season

2. Clinical studies

ADA109055: A 52-week, Randomized, Double-Blind, Parallel-Group Study of Fluticasone Propionate/Salmeterol DISKUS™ Combination Product (FSC) 250/50 mcg BID and Fluticasone Propionate (FP) DISKUS 250 mcg BID in Treatment of Subjects with Asthma

- **Methods:**

Objective: The primary objective was to demonstrate superiority of FSC DISKUS™ 250/50 BID over FP DISKUS 250 BID.

Study design: This was one of two duplicate multicenter randomized, parallel-group, double-blind, studies (ADA109055 and ADA109057) with ≤3 week open-label run-in period followed by a 52-week treatment period, conducted on an outpatient basis. A follow-up phone call was placed at 5 to 9 days after the last clinic visit.

Study population /Sample size: Male and female subjects ≥12 years old with a pre-bronchodilator FEV1 of ≥50% and ≤85% of predicted normal value, ≥12% FEV1 reversibility and a documented diagnosis of persistent asthma for at least 6 months. Subjects were to have experienced asthma symptoms requiring albuterol/salbutamol use within the 4 weeks preceding Screening and to be on treatment with a low-to-medium dose of an ICS or a combination of controller medications containing a low (total daily) dose ICS for at least 4 weeks preceding Screening. It was estimated that 289 subjects per treatment group would provide approximately 90% power for detection of a significant difference of 0.10 L in trough, pre-dose FEV1 change from baseline over the 52-week treatment period at a significance level of 0.05 based on a two sample two-sided t-test. It was also estimated that this sample size would provide approximately 80% power to detect a significant difference in the rate of asthma attacks in the FSC DISKUS 250/50 treatment group compared to the FP DISKUS 250 treatment group at the 0.05 significance level.

Treatments: Run-in period (14-21 days): FP DISKUS 100 one inhalation BID (open-label) Treatment period (52 weeks): FSC DISKUS 250/50 or FP DISKUS 250 one inhalation BID (1:1 ratio). All patients: Albuterol/salbutamol as needed.

Outcomes/endpoints: The primary efficacy endpoint was mean change from baseline in pre-dose FEV1. Secondary efficacy endpoints included morning peak expiratory flow (AM PEF), percentage of symptom-free days and asthma attack rate (per subject per year).

Statistical Methods: Statistical tests of all efficacy measures were two-sided alternative hypothesis tests conducted at the 0.05 significance level. For interpretation of results and to control overall type I error rate, step-down principles for testing of efficacy measures were implemented. The efficacy primary measure (mean change from baseline in pre-dose FEV1 over the 52- week treatment period) was compared between treatment groups using analysis of covariance (ANCOVA) including terms for treatment group, pooled investigator (geographic combination of sites) and baseline pre-dose FEV1 in the model.

- **Results**

Recruitment/ Number analysed: 621 subjects were included in the ITT Population: 306 in the FSC DISKUS 250/50 group and 315 in the FP DISKUS 250 group. 74% in the FSC DISKUS 250/50 group and 77% in the FP DISKUS 250 group completed the 52-week study. The most common reasons for withdrawal were voluntary subject withdrawal (8% in both groups) and protocol violation (FSC 7% and FP 8%). The total incidence of withdrawals due to lack of efficacy, or an exacerbation was low (≤1%). Withdrawal due to AEs occurred in 3% in the FSC group and in <1% in the FP group.

Baseline data: Patient demographics were similar between treatment groups. The majority of patients were female (63%) and White (65%). Mean age was ~38 years. A total of 75% of subjects had a duration of asthma for at least 10 years and 61% had a history of atopy. Mean percent predicted FEV1 was 68.9% at screening and 73.5% after the Run-in Period. Mean reversibility was 21.6%.

Efficacy results:

Primary endpoint: Over the 52-week treatment period, a greater mean increase from baseline in pre-dose FEV1 was observed in the FSC DISKUS 250/50 group (0.20 L) compared with the FP DISKUS 250 group (0.09 L) and the adjusted mean difference was statistically significant ($p<0.001$).

Secondary endpoints:

Symptom-free days: Over the 52 week treatment period, a greater mean increase in the percentage of symptom-free days was observed in the FSC DISKUS 250/50 group (37.1%) compared with the FP DISKUS 250 group (28.5%) and the adjusted mean difference was statistically significant ($p<0.001$).

PEF: Over the 52-week treatment period, a greater mean increase from baseline in AM PEF was observed in the FSC DISKUS 250/50 group (23.6 L/min) compared with the FP DISKUS 250 group (9.8 L/min) and the adjusted mean difference was statistically significant ($p<0.001$).

Asthma attack rate: The mean asthma attack rate (per subject per year) was lower in the FSC DISKUS 250/50 group (1.87) than in the FP DISKUS 250 group (2.14), but the treatment comparison ratio was not statistically significant ($p=0.2$).

Safety results: The overall incidence of AEs occurring during double-blind treatment was 78% in the FSC DISKUS 250/50 group and 79% in the FP DISKUS 250 group. URTI was the most commonly reported AE and occurred with a higher incidence in the FP DISKUS 250 group (30%) than in the FSC DISKUS 250/50 group (20%). All other common AEs occurred with a similar incidence between the treatment groups. The overall incidence of drug-related AEs was comparable between the treatment groups (8% with FSC DISKUS 250/50 and 9% with FP DISKUS 250). Oral candidiasis was the most frequently reported drug-related AE and occurred with an incidence of 2% in each treatment group. A total of 24 subjects experienced non-fatal SAEs post-randomization (during the treatment or follow-up periods), 14 subjects (5%) in the FSC DISKUS 250/50 group and 10 subjects (3%) in the FP DISKUS 250 group. Non-fatal SAEs that occurred in more than one subject were asthma exacerbation (3 subjects in the FSC DISKUS 250/50 group) and pneumonia (2 subjects in the FSC DISKUS 250/50 group).The incidence of withdrawals due to AEs was higher in the FSC DISKUS 250/50 group (10 subjects, 3%) compared with the FP DISKUS 250 group (3 subjects, <1%). AEs that led to withdrawal of more than one subject were headache (3 subjects in the FSC DISKUS 250/50 group) and cough (2 subjects in the FSC DISKUS 250/50 group).

Discussion and conclusion

This study demonstrated a statistically significant benefit in lung function measured as pre-dose FEV1 in the fluticasone propionate 250µg/salmeterol combination group compared to fluticasone propionate 250µg monotherapy (mean difference ~0.1L). The results of the secondary endpoints were in line with the primary endpoint. Generally, both treatments were well tolerated and the number of patients experiencing SAEs was low. No new significant findings are observed in this study, and no update of the SmPC is considered warranted.

ADA109057 - A 52-week, Randomized, Double-Blind, Parallel-Group Study of Fluticasone Propionate/Salmeterol DISKUS™ Combination Product (FSC) 250/50 mcg BID and Fluticasone Propionate (FP) DISKUS 250 mcg BID in Treatment of Subjects with Asthma

- **Methods:**

This study was a replicate of study ADA109055 described above.

- **Results:**

Recruitment/ Number analysed: 628 subjects were included in the ITT Population: 310 in the FSC DISKUS 250/50 group and 318 in the FP DISKUS 250 group. 75% in the FSC DISKUS 250/50 group and 74% in the FP DISKUS 250 group completed the 52-week study. The most common reasons for withdrawal were voluntary subject withdrawal (FSC=6%, FP=7%) and protocol violation (FSC=7%, FP=9%). Withdrawals due to lack of efficacy were comparable between the FP DISKUS 250 group (1%, 4 subjects) and the FSC DISKUS 250/50 group (<1%, 2 subjects). The incidence of withdrawals due to AEs was also similar between the treatment groups (2% in the FSC DISKUS 250/50 group, 3% in the FP DISKUS 250 group).

Baseline data: Patient demographics were similar between treatment groups. The majority of patients were female (58%) and White (82%). Mean age was ~40 years. A total of 71% of subjects had a duration of asthma for at least 10 years and a 54% had a history of atopy. Mean percent predicted FEV1 was 69.4% at screening and 73.9% after the Run-in Period. Mean reversibility was 23.2%.

Efficacy results:

Primary endpoint: Over the 52-week treatment period, a greater mean increase from baseline in pre-dose FEV1 was observed in the FSC DISKUS 250/50 group (0.16 L) compared with the FP DISKUS 250 group (0.12 L), however the adjusted mean difference was not statistically significant (p<0.09).

Secondary endpoints: The statistical plan for this study designated specific step-down rules for the testing of the secondary efficacy measures. Since a significant treatment difference was not observed for the analysis of the primary efficacy measure, all comparisons for the secondary measures were declared not statistically significant. However, the statistical results are provided to help inform on the outcome of the individual measures.

Symptom-free days: Over the 52-week treatment period, a greater increase in the percentage of symptom-free days was observed in the FSC DISKUS 250/50 group (37.4%) compared with the FP DISKUS 250 group (28.9%) and the adjusted mean difference was 8.0 (p=0.002 and was consistent with the AM PEF results).

PEF: Over the 52-week treatment period, a greater increase in AM PEF was observed in the FSC DISKUS 250/50 group (27.7 L/min) compared with the FP DISKUS 250 group (14.6 L/min) and the adjusted mean difference was 12.8 (p<0.001).

Asthma attack rate: The mean asthma attack rate (per subject per year) was slightly lower in the FSC DISKUS 250/50 group (2.73) than in the FP DISKUS 250 group (2.63), (p=0.7).

Safety results: The overall incidence of AEs occurring during double-blind treatment was

78% in the FSC DISKUS 250/50 group and 82% in the FP DISKUS 250 group. Nasopharyngitis was the most commonly reported AE and occurred with an incidence of 22% in the FP DISKUS 250 group and17% in the FSC DISKUS 250/50. All other common AEs occurred with a similar incidence in both treatment groups. The overall incidence of drug-related AEs was comparable between the treatment groups (8% in both groups). Candidiasis and cough were the most commonly reported drug-related AEs and each occurred with an incidence of 2% in the FP DISKUS 250 group and <1% in the FSC DISKUS 250/50 group. Two deaths occurred, one due to cardiac disease and one due to breast cancer. Neither event was considered drug related. A total of 14 subjects experienced non-fatal SAEs post-randomization, six in the FSC DISKUS 250/50 group and eight in the FP DISKUS 250 group. Three subjects in the FSC DISKUS 250/50 group and two subjects in the FP DISKUS 250 group were withdrawn due to their SAEs. Three of the non-fatal SAEs were considered related to study treatment by the investigators (Chest pain/syncope with FSC and asthma exacerbation with FP).

Discussion and conclusion

This study failed to demonstrate superiority of FSC DISKUS 250/50 over FP DISKUS 250 in increasing pulmonary function, as measured by the change from baseline in pre-dose FEV1 over a 52-week treatment period. Both treatments were well-tolerated and that FSC DISKUS 250/50 had an adverse event profile comparable to FP DISKUS 250. No new significant findings are observed in this study, and no update of the SmPC is considered warranted.

SAM101667 - A multicentre, randomized, double blind, parallel group study to compare the efficacy and safety of Salmeterol/Fluticasone propionate combination product (SERETIDE®) 50/100mcg with Fluticasone propionate (FLIXOTIDE®) 200mcg, both delivered twice daily via the DISKUS® inhaler, in the treatment of children aged 6-16 years with symptomatic asthma.

- **Methods**

Objective: The primary objective was to evaluate the non-inferiority of salmeterol/fluticasone propionate 50/100mcg bd in comparison with fluticasone propionate 200 mcg bd on symptom free days after 26 weeks of treatment.

Study design: This was a multi-centre, randomized, parallel-group, double-blind study in symptomatic children aged 6-16 years with asthma. The study consisted of three periods: a 4 week run-in period, a 26 weeks treatment period and a 2 week telephone follow-up call.

Study population /Sample size: Male and female subjects aged 6-16 years with a documented clinical history of asthma for at least 6 months and with bronchial hyperresponsiveness. Subjects must have used inhaled corticosteroids beclomethasone dipropionate, or budesonide up to 200 mcg bd, or have used fluticasone propionate at a dose of up to 125mcg bd for at least four weeks before the start of the run-in period. Furthermore, cumulative symptom score (day-time plus night-time) had to be totaling ≥ 14 in the last fourteen days of the run-in period. In total 300 subjects were planned for enrolment resulting in 152 (76/group) evaluable subjects at the end of the study. The subjects were equally divided between 2 treatment groups and were stratified for BHR, age and centre.

Treatment:
Run-in period (4 weeks): Fluticasone propionate 100 mcg bd. Treatment period (26 weeks): Salmeterol/ fluticasone propionate 50/100 mcg bd or fluticasone 200 mcg bd both via DISKUS. (1:1 ratio). All patients: Ventolin as needed.

Outcomes/endpoints: The primary efficacy endpoint was the percentage of asthma symptom free days during the last 10 weeks. Secondary endpoints included, the percentage of asthma symptom free days during 26 weeks, weekly mean symptom score during 26 weeks, lung function, RINT (in selected centers), FeNO (selected centers), bronchial hyperresponsiveness with PD20 methacholine, frequency of asthma exacerbations (discriminated on severity).

Statistical Methods: The study was designed to show non-inferiority of the SERETIDE arm in comparison with the FLIXOTIDE arm. Non-inferiority was considered to be shown if the upper limit of the one-sided 95% confidence interval of the difference µFLIXOTIDE minus µSERETIDE did not exceed +15% . (µFLIXOTIDE and µSERETIDE represent the mean percentages asthma symptom free days of the two respective treatment groups). The difference of the two mean values and its standard error was estimated using Repeated Measurements Analysis of Variance (SAS Proc Mixed with unstructured covariance matrix) while taking account of the baseline percentage of asthma symptom free days, age (<9 vs ≥ 9 years), centre and gender as covariates. Statistical tests of all efficacy measures were two-sided alternative hypothesis tests conducted at the 0.05 significance level.

- **Results**

Recruitment/ Number analysed: 158 subjects were randomized: 80 in the FSC DISKUS 100/50 group and 78 in the FP DISKUS 200 group. 74% in the FSC DISKUS 100/50 group and 77% in the FP DISKUS 200 group completed the study. A total of 7 subjects prematurely withdrew from the study, 6 in the FSC group for reason “other” and 1 in the FP group for “lack of efficacy”. No patients withdrew due to AEs. “Other” reasons included: lost-to-follow up (2 subjects), non-compliant with protocol (2 subjects), family problems (1 subject) and consent withdrawal (1 subject).

Baseline data: Patient demographics were similar between treatment groups. The majority of patients were male (FP=61%, SFP=54%). Mean age was 9.3 years (FP) and 9.4 years (SFP) and mean asthma duration was ~5.5 years (FP) and 5.7 years (SFP). There were no differences in the history of oral steroid courses in the previous year (FP=0.7, SFP =0.6). Most subjects (FP=72% and SFP=73%) did not have an exacerbation within the previous year that required hospitalization. Mean percentage of symptom free days were 15 in the FP group and 13 in the SFP group, and mean daily symptom score was 2.5 for FP and 2.3 for SFP. Mean percent predicted FEV1 was 100.7% for FP and 99.4% for SFP.

Efficacy results:

Primary endpoint: At week 16-26, non-inferiority of FSC vs FP was demonstrated (ITT population: adjusted difference FP-SFP by RmANOVA = +0.4 (95% CI = -9.1,9.9), p=0.63).

Secondary endpoints: For all the secondary endpoints there were no significant differences between treatment groups.

Safety results: A total of 121 patients (62 FP and 59 FSC) had at least 1 adverse event while being on treatment. This did not significantly differ between FP and FSC (p=0.930; chi-square

test). The most frequently reported AEs were common cold (SFP=35.9% vs FP 21.3%, p=0.062), headache (SFP=17.9% vs FP=26.3%, p=0.29) and sore throat (SFP=10.3% vs FP=7.5%, p=0.78).In 8 patients (3 FP, 5 SFC) an adverse event was judged by the investigator to be related to study medication. In each group there was one report of oropharyngeal candidiasis. A total of 5 subjects experienced a non-fatal SAE (3 FP and 2 FSC) throughout the complete study period (run-in to follow-up). Of these, there were 2 reports of worsening of asthma in the FSC group. The FP and FSC group did not differ for growth: mean statural growth for both groups was 2.9 cm in the 26 weeks period. Baseline adjusted difference between the FP and FSC group of the change from baseline in height SDS was –0.01 (95% CI: -0.05 to 0.04; p=0.76).

Discussion and conclusion

This study indicates that in children aged 6-16 years, a combination of salmeterol and a low dose of fluticasone propionate (100 mcg BD) achieves similar efficacy as a doubling of the dose of fluticasone propionate with regards to symptom control and lung function. Both treatments were well tolerated and the incidence of adverse events was similar in both groups. Based on the results of this study, an update of SmPC section 5.1 is considered warranted (see below).

ADA113872 - A Randomized, Double-Blind, Parallel Group study of FSC 100/50 and FP 100, both twice daily, in a Pediatric Population during the Fall Viral Season

- **Methods**

Objective: The primary objective of this exploratory study was to assess whether treatment with FSC DISKUS 100/50 mcg twice-daily results in a clinically meaningful decrease in the risk of asthma exacerbations during the fall season when compared with the same dose of ICS in FP DISKUS 100 mcg twice daily.

Study design: This was an exploratory 16-week multicenter, randomized, double-blind, parallel group study in pediatric subjects. One follow-up phone call was placed 7 days after the last clinic visit to assess for adverse events (AEs).

Study population /Sample size: Male and pre-menarchal female subjects aged 4 to11 years attending daycare or school with a documented diagnosis of asthma requiring ICS (as monotherapy or as part of a combination). Subjects were also required to have an AM PEF of ≥70% of predicted at Visit 1 and have a history of at least one exacerbation of asthma during the previous respiratory viral season that required the use of outpatient systemic corticosteroids, or an urgent care visit, ER visit, or hospitalization. Furthermore, their asthma must have been under control for the 3 months prior to randomization and they had to be candidates for stepdown therapy as outlined by current asthma management guidelines. Subject were withdrawn from the study if they had signs and symptoms of worsening asthma that required treatment with asthma medications other than study medication or oral/parenteral corticosteroids or had more than 2 asthma exacerbations. A sample size of 150 subjects per treatment was chosen to support the nature of asthma exacerbations as infrequently-occurring events. However, because of the descriptive nature of this study, there were no formal power or sample size calculations.

Treatment:
FSC DISKUS 100/50 mcg, one inhalation twice daily or FP DISKUS 100 mcg, one inhalation twice daily. All patients: Albuterol inhalation aerosol as needed.

Outcomes/endpoints: The primary efficacy endpoint was the number of exacerbations of asthma from the start of double-blind treatment until the end of treatment (Week 16). Secondary efficacy endpoints were based on the peak viral period (from 30 August 2010 through the end of the double-blind treatment period) and included severity of asthma symptoms, duration of worsening asthma symptoms and incidence of exacerbations associated with the presence of moderate or severe upper respiratory tract symptoms, a confirmed rhinovirus (RV) infection, or both, asthma control days, episode-free days (an asthma control day plus daily peak flow ≥80% of baseline), rescue-free days and asthma symptom-free days.

Statistical Methods: Analyses were performed using the Intent-to-Treat (ITT) Population. Due to the exploratory nature of this study, no formal hypothesis tests were proposed with respect to any exacerbations measures. However, treatment differences were assessed statistically in terms of asthma control days, episode-free days, symptom-free days, and rescue-free days. Statistical comparisons of each of these types of days included a term for center identifier in the models. No covariates were included. No corrections for multiple comparisons or multiplicity were required. Kaplan-Meier estimates, adjusted for center, and Cox Proportional Hazard models were used to provide a time-adjusted estimate of the probability and risk of having an asthma exacerbation while receiving FSC treatment compared with FP treatment.

- **Results**

Recruitment/ Number analysed: A total of 339 subjects (171 FSC group and 168 FP group) were treated at 39 centers in the US. Most subjects (86% in both groups) completed the study. Of the 47 subjects who withdrew, the most common primary reasons for withdrawal were subject withdrew consent (FP n=10, FSC n=6) and protocol deviation (FP n=3, FSC n=10). Few subjects in the study population were withdrawn due to AEs or lack of efficacy (total 3 subjects each).

Baseline data: Demographics were comparable between the treatment groups. The majority of subjects were White (76%) and male (65%). Mean age was 7.4 years. Most subjects (91%) were attending traditional school which had not started yet at the time of randomization. The mean duration of asthma was 4.6 years (range: 0.4 year to 11 years) and 88% of subjects had not been exposed to passive smoke. Most subjects (93%) did not have an exacerbation within the previous year that required hospitalization. The majority of subjects (69%) had one exacerbation that required oral corticosteroids or antibiotics.

Efficacy results:

Primary endpoint: The proportion of subjects experiencing an asthma exacerbation was 12% in both groups. The mean duration of the exacerbation was similar between the treatment groups (8.3 days in the FSC group and 7.9 days in the FP group). The probability of having an asthma exacerbation during the double-blind treatment period was 13.3% (95% CI: 8.9, 19.7) in the FSC group and 19.1% (95% CI: 9.2, 37.4) in the FP group (HR= 0.971, p=0.928).

Secondary endpoints:

Asthma exacerbations during the peak viral period: The total number of asthma exacerbations reported during the peak viral period was 11% in both groups. Few asthma exacerbations were

associated with upper respiratory symptoms or confirmed rhinovirus infection during the peak viral period (FSC n=5, FP n=7). The mean duration of the exacerbations associated with upper respiratory symptoms or rhinovirus infection was 1.1 days longer in the FSC group (8.2 days) compared with the FP group (7.1 days). The probability of having an asthma exacerbation associated with upper respiratory symptoms or confirmed rhinovirus infection during the peak viral period was 3.2% (95% CI: 1.3, 7.4) in the FSC group and 5.3% (95% CI: 2.5, 11.2) in the FP group (HR=0.598, p=0.385).

Symptom scores: Baseline asthma symptom scores were low and similar between the treatment groups (mean of 0.2 and median of 0 in both the FSC and FP groups). Compared with baseline, mean asthma symptom scores were higher on the day of upper respiratory symptoms or confirmed rhinovirus infection (1.0 in the FSC group and 0.9 in the FP group). The mean number of days with an upper respiratory symptom score of 2 (moderate) or 3 (severe) was low and similar between the treatment groups (2 days in each treatment group).

Asthma control days: The mean percentage of asthma-control days, episode-free days, symptom-free days, and rescue-free days was similar between the FSC and FP groups and none of the treatment differences were statistically significant. Both treatment groups on average had >90% of symptom-free and rescue-free days and nearly 50% asthma control days.

Safety results: The overall incidence of AEs was similar between the treatment groups, 65% in the FSC group and 67% in the FP group. The most common AEs included: URTI, headache, cough, pyrexia, and nasopharyngitis. The incidence of individual AEs was similar between the treatment groups with the exception of sinusitis, which was more frequent in the FSC group (11 subjects, 6%) compared with the FP group (3 subjects, 2%) and otitis media which was more common with FP (9 subjects, 5%) than with FSC (3 subjects, 2%). The overall incidence of AEs considered drug-related by the investigators was low and comparable between the treatment groups, 8% FSC group and 6% FP group. The most common drug-related AEs were headache and URTI (occurring in a total of 5 subjects each). Five non-fatal SAEs were reported for 3 subjects during the study, 2 subjects in the FSC group and 1 subject in the FP group.

Discussion and conclusion

This study showed no significant treatment difference between FSC 100/50 mcg and FP 100 mcg administered twice daily in the risk of asthma exacerbations during the fall viral season in pediatric subjects aged 4 to 11 years with mild asthma. Other efficacy endpoints and health outcome measures also showed no clinically relevant differences between the two treatments in this study population. Both treatments were well tolerated and the incidence of AEs was similar for the two products. Whereas generally a benefit of combination treatment vs treatment with fluticasone propionate monotherapy would be expected, the lack of a between group difference could be explained by the exploratory nature of the study (i.e. no formal power calculations were done) and the low proportion of patients experiencing an exacerbation (12%). No significant new findings were observed indicating a need to update the SmPC.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

Four studies were submitted within this article 46 paediatric work sharing procedure. The results of one study (SAM101667) is considered to provide relevant information on the use of salmeterol/fluticasone propionate in the paediatric population and thus an update of SmPC section 5.1 with the results of this study is considered warranted.

- **Recommendation**

Section 5.1 of the SmPC should be updated with the following wording:

"In trial SAM101667, in 158 children aged 6-16 years with symptomatic asthma, the combination of salmeterol/fluticasone propionate is equally efficacious to doubling the dose of fluticasone propionate regarding symptom control and lung function. This study was not designed to investigate the effect on exacerbations."

A Type IB variation is requested from the MAH by the end of June 2013.